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2024 American College of Rheumatology (ACR) Guideline for the Screening, Treatment, and Management of Lupus Nephritis

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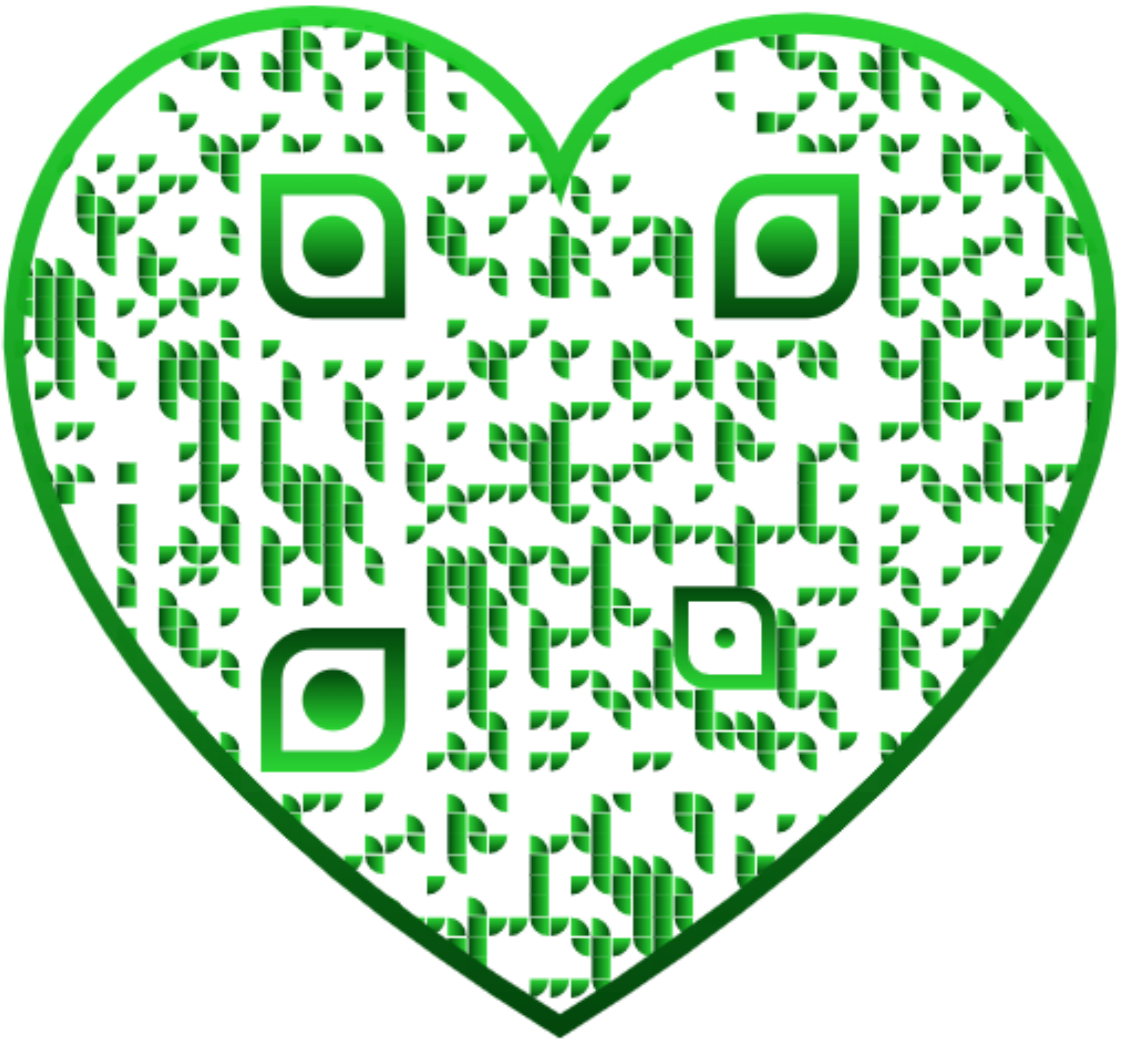
A feature designed to facilitate discussion of published research. This slide presentation accompanies the below article:

Sammaritano LR, Askanase A, Bermas BL, et al. 2024 American College of Rheumatology (ACR) Guideline for the Screening, Treatment, and Management of Lupus Nephritis. Arthritis Care Res (Hoboken) 2025. https://doi.org/10.1002/acr.25528



Background

- The American College of Rheumatology last published lupus nephritis guidelines in 2012 and recommended high-dose glucocorticoids with mycophenolate or cyclophosphamide for induction therapy, with mycophenolate maintenance therapy.
- The emergence of positive data on new therapies led to the need for updated guidelines.
- The current guideline focuses on lupus nephritis but was part of a larger effort that also included recommendations for the management of SLE (separate GL/manuscript).
- These guidelines can be interpreted in the context of guidelines from the European Alliance of Associations for Rheumatology (EULAR) and Kidney Disease Improving Global Outcomes (KDIGO).

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Methods

- GRADE methodology used to develop recommendations
- Developed 249 PICO (Population-Intervention-Comparator-Outcome) questions related to lupus nephritis
- Systematic literature review performed to generate evidence summaries
- Patient panel (n=14) convened to help define patient values and preferences
- Voting panel (n=21) including adult and pediatric rheumatologists, adult and pediatric nephrologists, and patients (2) voted on the direction and strength of recommendations, requiring ≥70% agreement

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GRADE process

Evidence synthesis

Formulate question

P
I
C
O

Select outcomes

Rate importance

- Outcome — Critical
- Outcome — Critical
- Outcome — Important
- Outcome — Not important

Outcomes across studies

Create evidence profile with GRADEpro

Summary of findings & estimate of effect for each outcome

Rate quality of evidence for each outcome

- High
- Moderate
- Low
- Very low

Randomization raises initial quality
RCTs: high
Observational: low

Grade down

1. Risk of bias
2. Inconsistency
3. Indirectness
4. Imprecision
5. Publication bias

Grade up

1. Large effect
2. Dose response
3. Opposing bias & confounders

Grade overall quality of evidence across outcomes based on lowest quality of ***critical*** outcomes

Panel

Patient panel

Recommendation

Grade recommendations (Evidence to Recommendation)

1. For or against (direction) ↓↑
2. Strong or conditional (strength)

By considering balance of consequences (evidence to recommendations):

- Quality of evidence
- Balance benefits/harms
- Values and preferences
- Feasibility, equity and acceptability
- Resource use (if applicable)

Guideline

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Methods

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Factors influence strength of a recommendation:

- Quality of evidence
- Degree of certainty on balance of harms and benefits
- Whether recommendations are particularly sensitive to different patient values/references

Implications of a strong recommendation

- **Population**: Most people in this situation would want the recommended course of action and only a small proportion would not
- **Health care workers**: Most people should receive the recommended course of action

Implications of a conditional recommendation

- **Population**: The majority of people in this situation would want the recommended course of action, but many would not
- **Health care workers**: Be prepared to help people to make a decision that is consistent with their own values/decision aids and shared decision making

Guiding Principles

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PRESERVE KIDNEY FUNCTION AND MINIMIZE MORBIDITY / MORTALITY FROM CKD AND TREATMENT

ENSURE COLLABORATIVE CARE WITH NEPHROLOGY

UTILIZE SHARED DECISION-MAKING INCLUDING PATIENT VALUES AND PREFERENCES

AIM TO REDUCE HEALTHCARE DISPARITIES

CONSIDER PEDIATRIC AND GERIATRIC POPULATIONS

28 graded recommendations (7 strong, 21 conditional), 13 ungraded Good Practice Statements (GPS)

Apply to all patients with LN regardless of age, race, ethnicity, other patient variables. No recommendations are based on race or ethnicity as evidence is limited/confounded by socioeconomic factors.

Therapeutic decisions:

- Vary - depending on clinical presentation/patient preferences
- May be limited - by access to specialists, procedures, and medications
- Available traditional therapies should be used if recommended medications are not available or not preferred by patients

Results

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From Table 3

- **Screening: check proteinuria q6-12 mo. or at time of clinical flare for all patients with SLE without known LN (S)**
- **Suspected Lupus Nephritis:**
  - **Perform kidney biopsy promptly (GPS)**
  - **Treat promptly with glucocorticoids (while awaiting a kidney biopsy and the histopathology results) (GPS)**
- **Kidney biopsy for:**
  - **SLE with urine Pr:Cr >0.5 g/g -or- unexplained impaired kidney function (C)**
  - **In patients with known lupus nephritis for:**
    - **Suspected flare OR**
    - **Lack of response/worsening after 6 months of therapy (C)**
- **Hydroxychloroquine for all pts (S)**
- **RAAS-I for all pts with elevated proteinuria (even <0.5 g/g) (C)**
- **Adjust lupus nephritis medication dosages in patients with decreased GFR (GPS)**

S: strong recommendation C: conditional recommendation GPS: Good Practice Statement

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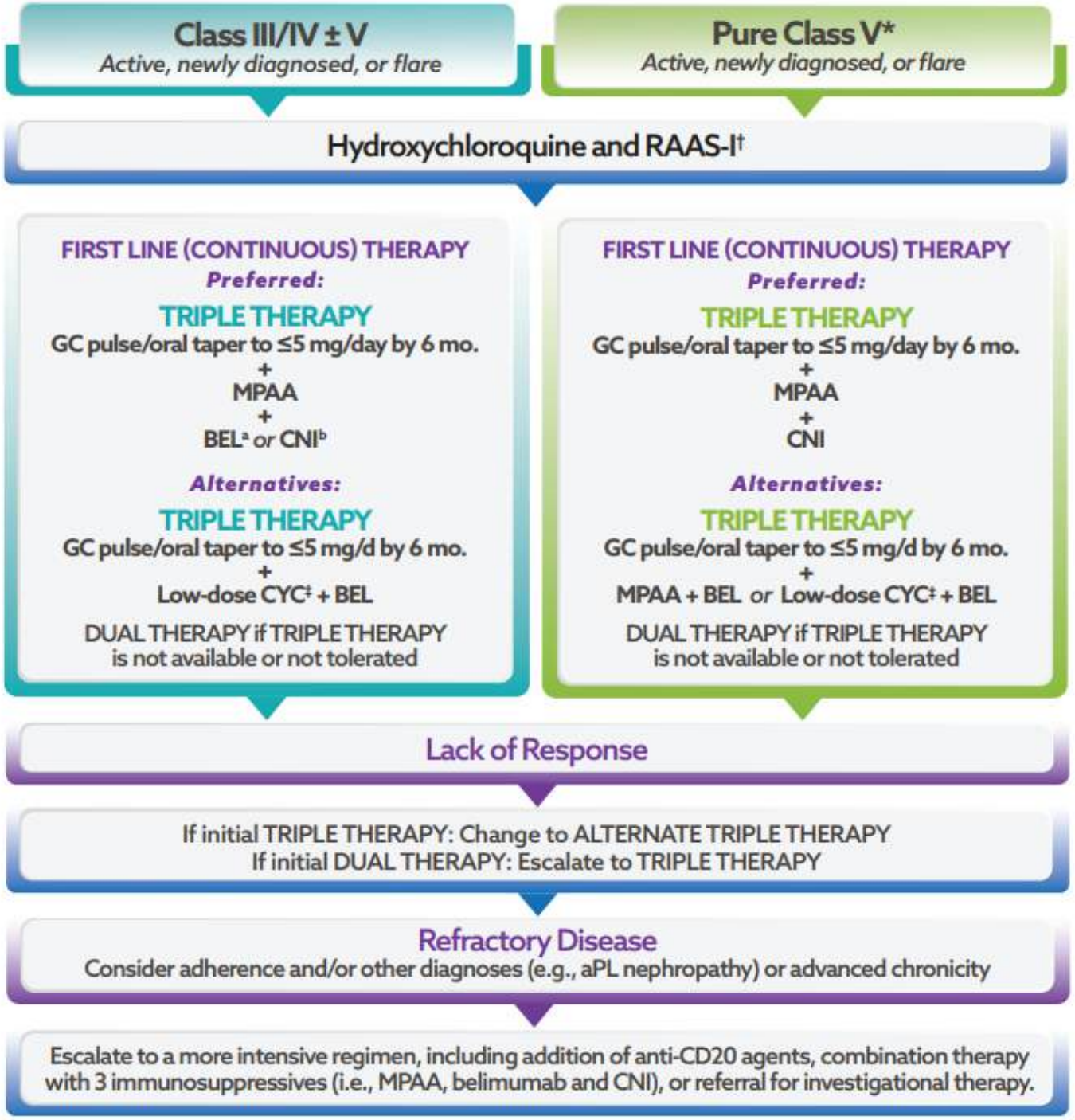
Guideline Summary

Goal: Complete renal response (CRR)
- Within 6-12 mo., reduction in proteinuria to ≤0.5 g/g and
- Stabilization or improvement in kidney function (±20% baseline)

Duration of therapy: at least 3-5 years after achievement of CRR

* For ≥1 g protein; for <1 g, treat with GC and/or immunosuppression.
† Discuss adjunctive treatment with systemic anticoagulation with nephrology for patients with LN and significant factors for thrombosis (eg, low serum albumin in context of severe proteinuria).
‡ Substitute MPAA once low-dose CYC cycle is completed.
a: Recommended preferentially when significant extrarenal manifestations are present.
b: Recommended preferentially when proteinuria is ≥3.0 g.

GC pulse/oral taper: pulse intravenous GCs (250–1,000 mg methylprednisolone daily for 1–3 days) followed by oral GC ≤0.5 mg/kg/day (maximum dose 40 mg/day) and taper. Low-dose CYC: as per Euro-Lupus Nephritis Trial protocol, 500 mg IV CYC every 2 weeks for 6 doses. Dual therapy: GC plus/oral taper plus one immunosuppressive agent, usually MPAA or low-dose CYC. RAAS-I, renin-angiotensin-aldosterone system inhibitors; GC, glucocorticoid; MPAA, mycophenolic acid analogs (including mycophenolate mofetil [MMF]; BEL, belimumab; CNI, calcineurin inhibitor; CYC, cyclophosphamide.


Class III/IV ± V
Active, newly diagnosed, or flare
Pure Class V*
Active, newly diagnosed, or flare
Hydroxychloroquine and RAAS-I†
FIRST LINE (CONTINUOUS) THERAPY
Preferred:
TRIPLE THERAPY
GC pulse/oral taper to ≤5 mg/day by 6 mo.
+
MPAA
+
BEL[a] or CNI[b]
Alternatives:
TRIPLE THERAPY
GC pulse/oral taper to ≤5 mg/d by 6 mo.
+
Low-dose CYC‡ + BEL
DUAL THERAPY if TRIPLE THERAPY is not available or not tolerated
FIRST LINE (CONTINUOUS) THERAPY
Preferred:
TRIPLE THERAPY
GC pulse/oral taper to ≤5 mg/day by 6 mo.
+
MPAA
+
CNI
Alternatives:
TRIPLE THERAPY
GC pulse/oral taper to ≤5 mg/d by 6 mo.
+
MPAA + BEL or Low-dose CYC‡ + BEL
DUAL THERAPY if TRIPLE THERAPY is not available or not tolerated
Lack of Response
If initial TRIPLE THERAPY: Change to ALTERNATE TRIPLE THERAPY
If initial DUAL THERAPY: Escalate to TRIPLE THERAPY
Refractory Disease
Consider adherence and/or other diagnoses (e.g., aPL nephropathy) or advanced chronicity
Escalate to a more intensive regimen, including addition of anti-CD20 agents, combination therapy with 3 immunosuppressives (i.e., MPAA, belimumab and CNI), or referral for investigational therapy.

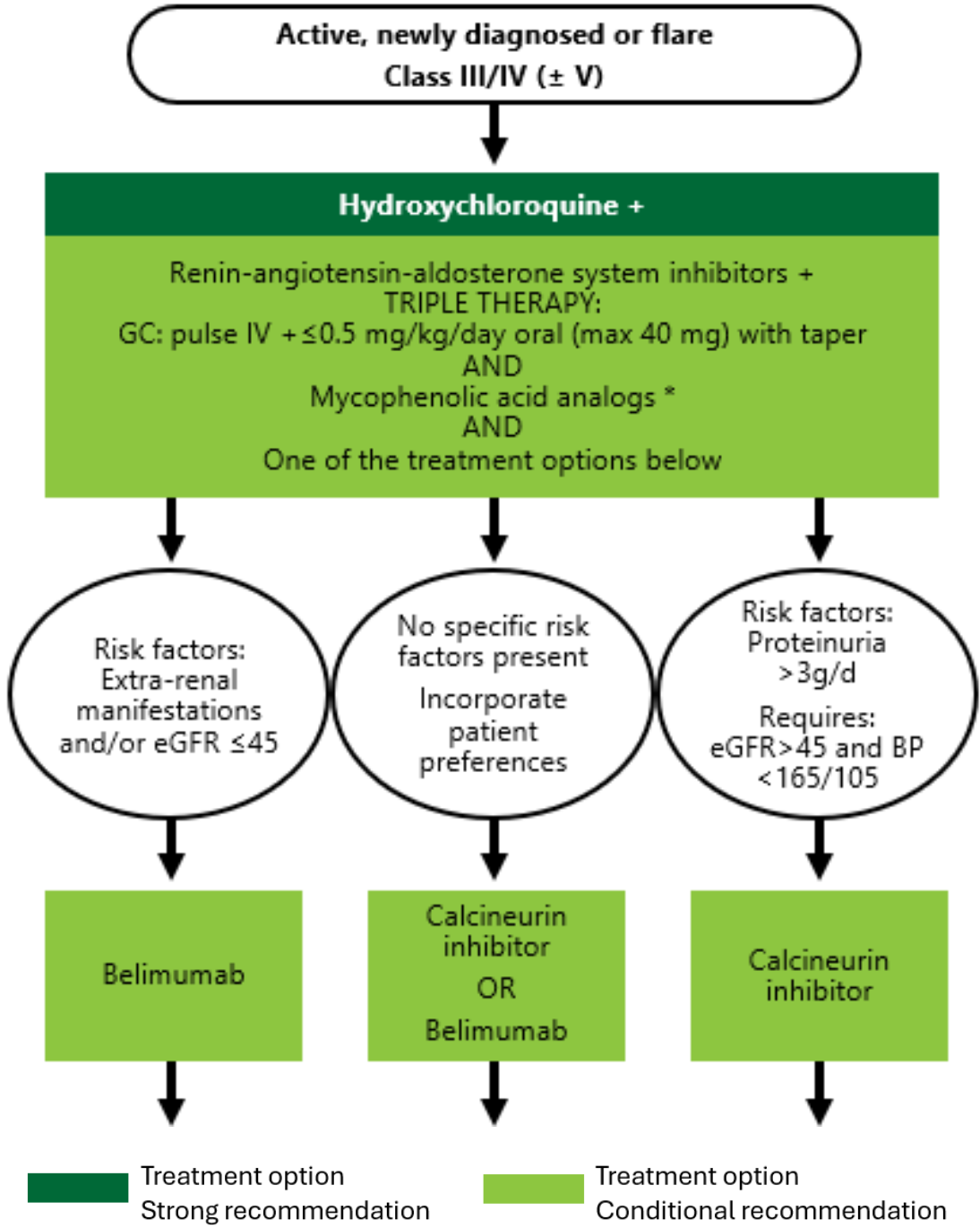
Results

Figure 1: Class III/IV nephritis treatment

- Hydroxychloroquine (strong), RAAS inhibitor for any increased proteinuria
- "Triple therapy":

1. Glucocorticoids:
   - Pulse IV 250-1000mg/day × 1-3 days, then
   - Oral prednisone ≤0.5mg/kg/day (max 40mg) with taper to ≤5mg by 6 months
2. Mycophenolate (preferred over cyclophosphamide)
3. Belimumab or calcineurin inhibitor (CNI) *

*GL does not recommend a particular CNI because comparative effectiveness and safety studies are not available.



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Results

- Why triple therapy for Class III/IV nephritis?
  - RCTs (BLISS-LN and AURORA 1) showed improved outcomes with initial triple versus initial dual therapies → guided Voting Panel discussion, along with Patient Panel input and clinicians' experience
- Mycophenolate + belimumab preferred: if there are significant extrarenal manifestations (or CrCl<45, significant HTN given potential nephrotoxicity and HTN from CNI)
- Mycophenolate + calcineurin inhibitor (cyclosporine, tacrolimus, voclosporin) preferred: for proteinuria ≥3 g/g
- If cyclophosphamide is used, prefer Euro-Lupus Nephritis Trial low-dose CYC 500 mg IV q2 weeks × 6 doses (then mycophenolate)
  - For triple therapy, can be combined with belimumab (limited data from BLISS-LN)
  - Combination with calcineurin inhibitor not studied in RCTs

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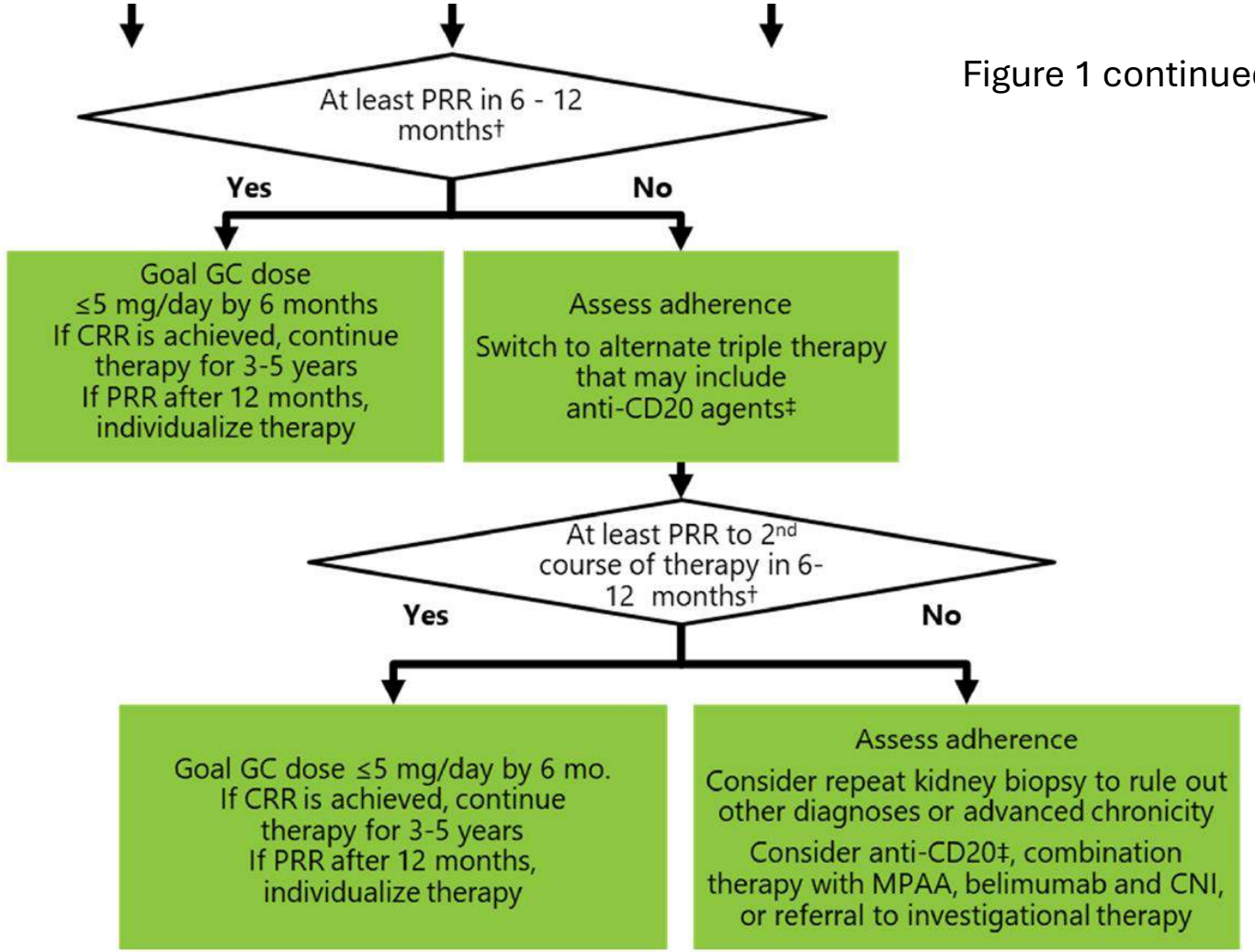
Results

Figure 1 continued:

- If not achieving partial renal response (PRR)
  - Assess adherence
  - Switch to alternative triple therapy
- If continued lack of partial renal response
  - Consider repeat kidney biopsy
  - Alternative combinations
  - Consider clinical trial

Figure 1 continued


At least PRR in 6 - 12 months†
Yes
No
Goal GC dose ≤5 mg/day by 6 months If CRR is achieved, continue therapy for 3-5 years If PRR after 12 months, individualize therapy
Assess adherence
Switch to alternate triple therapy that may include anti-CD20 agents‡
At least PRR to 2nd course of therapy in 6-12 months†
Yes
No
Goal GC dose ≤5 mg/day by 6 mo. If CRR is achieved, continue therapy for 3-5 years If PRR after 12 months, individualize therapy
Assess adherence
Consider repeat kidney biopsy to rule out other diagnoses or advanced chronicity
Consider anti-CD20‡, combination therapy with MPAA, belimumab and CNI, or referral to investigational therapy

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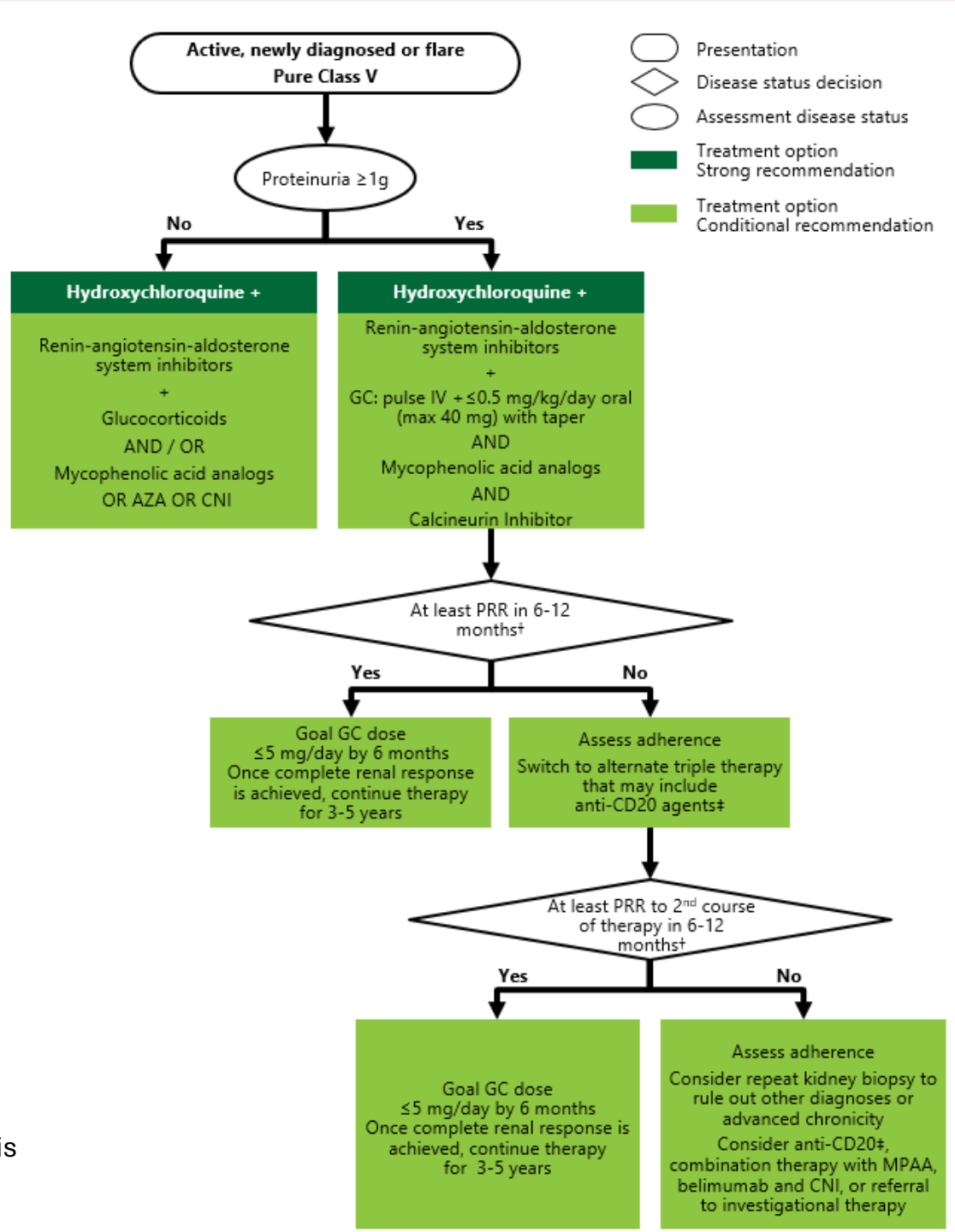
Results

Figure 2: Class V nephritis treatment

- Hydroxychloroquine (strong)
- RAAS inhibitor (any level of increased proteinuria)
- Treatment depending on degree of proteinuria
  - ≥1g → triple therapy with glucocorticoids, mycophenolate, calcineurin inhibitor
  - <1g → glucocorticoids and/or mycophenolate OR azathioprine OR calcineurin inhibitor
- Assess adherence and switch therapy if lack of at least partial renal response



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Results

Total therapy duration for patients with complete renal response: at least 3-5 years

- **Goal**: rapid control of disease activity and continued therapy until sustained inactive disease
- Repeat biopsy studies show immunologic activity/immune complexes persisting in the kidneys for several years
- Withdrawal of immunosuppression while histologic activity remains predisposes patients to LN flare
- Over time, immunosuppressive therapy may be tapered, as determined by renal and extra-renal disease activity and medication tolerability

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Results

- Other considerations, including cardiovascular health, bone health, infection risk, and reproductive health concerns were not voted on, but general suggestions for care are offered.
- Good practice guidance and references to other ACR guidelines are summarized in Table 4.

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Discussion

- Many conditional recommendations – apply to many patients but decisions may be sensitive to individual circumstances and patient values/preferences – requires shared decision making.
- Recommendations for a lower glucocorticoid regimen aim to reduce toxicity but are not based on RCTs directly comparing different glucocorticoid regimens.
- RCTs of triple therapy suggested improved renal outcomes, but data on long-term renal outcomes (i.e., need for ESRD) are currently limited. Information on which patients are most likely to benefit from triple therapy vs. dual therapy is also limited.
- RCT evaluating addition of obinutuzimab to standard therapy was published after these guidelines; will be considered in future guidelines.
- No consensus for treatment of Class II lupus nephritis, and no recommendations for lupus podocytopathy.

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Discussion

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Discussion questions:

- How do recommendations for glucocorticoid taper compare to your current practice? Will these recommendations change how you prescribe glucocorticoids?
- Will recommendations for triple therapy change your practice? What factors might affect your decision to suggest triple therapy for an individual patient?
- Are there other ways these guidelines will change how you diagnose or treat patients with lupus nephritis?
- What do you think are the key next research steps?

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